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Evaluation of the efficacy of Mecobalamine (Vit B12) in the treatment of long-term pain in women diagnosed with fibromyalgia: Randomized controlled trial protocol

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3 **Evaluation of the efficacy of Mecobalamine (Vit B12) in the treatment of**
4 **long-term pain in women diagnosed with fibromyalgia: Randomized**
5 **controlled trial protocol**
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ABSTRACT

Introduction

Fibromyalgia causes long term pain. It affects at least 2% of the population, the majority being women. In addition, extended symptoms corresponding to vitamin B12 deficiency occur. Primary studies indicate interaction effects between the receptor of NMDA which is involved in both long-term pain and vitamin B12 deficiency. The aim of the proposed study is to evaluate whether vitamin B12 decreases pain sensitivity and the experience of pain i.e. hyperalgesia and allodynia in women suffering of fibromyalgia.

Methods and analysis

The study is a randomised placebo-controlled (RCT), single-blind, clinical trial with two parallel groups who are administered Mecobalamin (vitamin B12) v/s placebo over 12 weeks. Outcomes consist of questionnaires and QST measured at baseline and after 12 weeks of treatment. A final re-evaluation will then follow 12 weeks after treatment ends. In order to broaden the understanding of the lived experience, an interview is conducted using a phenomenological approach on a life-world theoretical basis, the Reflective Lifeworld Research approach (RLR).

Ethics and dissemination

The protocol for the study is approved by the local ethical committee at Linköping (EPM); 2018/294-31 (Appendix 2019-00347; 2020-04482), and the Swedish Medical Products Agency; EudraCT-no 2015-005086-23 (Appendix 5.1-2020-71076). The study started 6 of February 2019, recruiting is delayed caused by COVID-19. Trial results expects during 2024 and will primarily be communicated through peer-reviewed journals and conferences.

Title registration: EUDRACT 2015-005086-23

ClinicalTrials.gov: ID NCT05008042

Keywords: Fibromyalgia, Cobalamin, Chronic pain, Mekobalamin, Randomised controlled trial, Vitamin B12

STRENGTH AND LIMITATION OF THIS STUDY

- The trial is a collaboration between different universities and regions.
- To the best of our knowledge, this is the first trial that specifically examined the effect of Mecobalamin (Vitamin B12) on pain in the current patient group, women diagnosed with fibromyalgia.
- The recruitment period will likely be delayed by COVID-19.

INTRODUCTION

Fibromyalgia causes long-term pain and affects at least 2% of the population, 80% of the sufferers being women (1). Treatment options are scarce and patients with fibromyalgia have experienced being discredited and invalidated by the health-care system (2). Fibromyalgia is characterized by long-term widespread musculoskeletal pain and generalized hyperalgesia. This is often accompanied by fatigue, concentration problems and sleep problems (3). Fibromyalgia pain is currently classified as nociplastic, which means that pain arises from altered regulation of pain signals, in absence of tissue damage (4).

No definite pathophysiology has been established for fibromyalgia. Imaging techniques have challenged previous ideas about the peripheral origin of FM and have provided evidence for altered central nervous system (CNS) nociceptive/pain processing and morphology in fibromyalgia. Furthermore, recent studies report both central alterations and peripheral alterations (e.g., systemic low-grade inflammation and nociceptor/muscle alterations) (5-9)

The treatment for Fibromyalgia includes both non-pharmacological and pharmacological interventions, depending on the key symptoms and the extent of disability. The recommended pharmacological treatments for Fibromyalgia are antidepressants (e.g. SNRI) and antiepileptics (e.g. gabapentinoids), which often bring side effects (4). In addition, opioid analgetics and NSAID/COX are often prescribed (10). However, only a

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3 minority of individuals report a clinically relevant improvement from any of
4 the treatments (11).
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8 Vitamin B12 is sometimes used for symptoms other than those of Vitamin
9 B12 deficiency for example, different pain conditions such as backpain and
10 neuropathic pain (12-16). Vitamin B12 nasal drops have also been tested and
11 shown positive results on patients with ME/CF/fibromyalgia (myalgic
12 encephalomyelitis/chronic fatigue syndrome) (17). In addition, there are
13 Vitamin B12 studies that have shown good results in the therapy of aphthous
14 ulcers (18) and acute lumbago (19) as well as in studies concerning diabetic
15 polyneuropathy (20, 21). Moreover, there are studies that examined
16 methylcobalamin treatment on patients with lower back pain showing pain
17 reduction and functionality gain (13, 22).
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27 To summarize, it is not entirely clear how Vitamin B12 affects the human
28 pain system. However, several studies indicate that it may be a possible
29 treatment in fibromyalgia.
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33 **Aim and objectives**

34 The aim of this study is to evaluate the effect of Mecobalamin (Vitamin
35 B12), and describe lived experiences of pain, health, suffering and well-
36 being in women with diagnosed fibromyalgia.
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43 The primary objective is to evaluate whether Mecobalamin (Vitamin B12)
44 given as an intramuscular injection once/week for 12 weeks compared to
45 placebo reduces pain sensitivity i.e. tolerance time (Cold Pressor Test).
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48 The secondary objective is to evaluate whether intramuscular Mecobalamin
49 (Vitamin B12) compared to placebo reduces pain intensity and pressure pain
50 threshold (Numeric rating scale NRS, Pressure Algometry), increases activity
51 level (questionnaire), quality of life (questionnaire) and perceived effect of
52 given drug (questionnaire). Furthermore, the ratings of expected effects of a
53 given drug (NRS), the desire for pain relief (NRS) and estimated pain
54 variability (NRS) are evaluated. Qualitative interviews that describe how
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women with fibromyalgia experience pain, health, suffering and well-being (interviews) will be conducted.

METHODS AND ANALYSIS

Study design

The study is a randomised placebo-controlled (RCT) single-blind clinical trial using parallel groups. Participants are individually randomised to intervention or control group (placebo) in 1:1 allocation. In order to broaden and deepen the understanding of the lived experience, an interview will be conducted applying a phenomenological approach on a life-world theoretical basis, Reflective Lifeworld Research approach (RLR) (23).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Study sample

Women aged 20-70 years with an earlier recorded diagnosed fibromyalgia. Detailed eligibility criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none"> - Diagnosis of fibromyalgia - Women aged 20-70 years - Swedish-speaking - Safe method of contraception - Cobalamin value >250 pmol/L < 800 pmol/L - Kidney function value (relatively) GFR >60 mL/min/1.73 m² - Liver function value P-ALP 0.6-2.85 µkat/L - P-ALAT 0.15-1.13 µkat/L - Heart function value Troponin-T < 15 ng/L - NT-pro-BNP < 60 year <125 ng/L 	<ul style="list-style-type: none"> - Previous treatment with B12 - Known hypersensitivity to the active substance Mecobalamin or an additive - Neuroleptic treatment - Reynaud's phenomenon - Known neuropathy - Vegan as veganism can lead to B12 deficiency - Known heart, kidney or liver disease - Breastfeeding - Planned or ongoing pregnancy

NT-pro-BNP > 60 year < 300 ng/L - Given consent to participate	
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The participants are recruited via advertising in the local newspaper Facebook, YouTube, Fibromyalgia Association, posters at Linnaeus University, hospitals and healthcare centres. The prospective participant contacts the Trial Manager via telephone or email and receives oral information. Written information and consent form are sent to the participant who contacts the Trial Manager for an appointment.

Intervention and placebo to be measured

The active substance of Vitamin B12 given in the study is Mecobalamin 5mg/ml 2 ml i.e. 10 mg intramuscularly (24). Placebo substance is Sodium Chloride (NaCl) 9 mg/ml 2 ml, isotonic solution for parenteral use (Baxter) intramuscularly (25). All participants are informed that their urine may turn red, which may occur during Mecobalamin injections.

Measurements

At the first measurement opportunity, the trial manager and co-examiner 1 carefully goes through inclusion and exclusion criteria. Oral information is given again, and consent is signed by the participant and by the co-examiner 1. First, the participant answers two questionnaires Short-form McGill Pain Questionnaire (MPQ) (26) and RAND 36 (27), then stimulation tests (Cold Pressor Test, pressure algometry) (28 - 32) are performed followed of pain rating (NRS) (33) immediately, after one minute and after three minutes. Finally, blood samples for cobalamin (Vitamin B12), kidney, liver and heart function are taken. The participant provides a wrapped information card about the study's design, purpose, treatment options and contacts with telephone numbers. The participant is asked about interest in an interview in connection with the final measurement opportunity. Co-examiner 2 assesses the blood samples and approves final inclusion. If tests deviate from accepted reference values, the participant is excluded and encouraged to seek medical attention.

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3 After approved inclusion, an independent chief examiner performs the
4 randomisation. The participant then receives intramuscular injections of the
5 active substance or placebo, once a week for 12 weeks, given by a registered
6 nurse. Before each injection the participant answers questions in which they
7 estimate their expected effects of a given drug, desire for pain relief and
8 average pain intensity during the past week (NRS). The participant has the
9 opportunity to postpone the visit \pm 3 days, for example in case of illness or
10 travelling and may miss a maximum of two injections in order to follow per
11 protocol analysis. Even if the participant is not compliant with the study
12 protocol, the participant may retain the treatment regime for the duration of
13 the study and be analysed in Intention to Treat (ITT).
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24 The second measurement takes place after 12 weeks of intervention and three
25 questionnaires (MPQ, RAND 36) and (Patient Global Impression of Change
26 PGIC) (34) are filled in. The stimulation tests Cold Pressor Test and pressure
27 algometry are performed as well as blood sampling of cobalamin/p (Vitamin
28 B12). In cases of low cobalamin/p, the participant is encouraged to seek
29 medical attention but is still included in the study.
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36 At the third measurement, the follow-up, which takes place 12 weeks after
37 the end of the intervention, the participant fills in questionnaires (MPQ,
38 RAND-36 and PGIC), undergoes stimulation tests (Cold Pressor Test and
39 pressure algometry), blood sampling of cobalamin/p (Vitamin B12) together
40 with an interview for those who so desire. If cobalamin/p on this occasion
41 shows that the participant has a low cobalamin value, the participant is
42 encouraged to seek medical attention. For the individual participant, the
43 study ends after six months. An overview of the study flow is presented in
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Outcomes

The primary outcome is

- Tolerance time, maximised to three minutes, which is tested using the Cold Pressor Test

The secondary outcome are;

- Pain experience and possible pain reduction measured by a pressure algometry test performed on the shoulder, hip, knee and elbow.
- The pain intensity measured by NRS.
- Ratings of expectation, desire for pain relief, and pain variability using NRS.
- Activity level and quality of life assessed using questionnaires MPQ and RAND-36.
- Experience of the effect of the drug assessed using questionnaire PGIC.
- Control of Vitamin B12 by measuring cobalamin in plasma.
- Qualitative in-depth interviews conducted to capture women's lived experiences of pain, health, suffering and well-being.

Cold Pressor Test

The Cold Pressor Test (28-30) is measured in number of seconds the participant leaves her hand in the low-temperature water of five degrees. Evaluation variables from Cold Pressor Test become pain threshold (when it starts to hurt) and tolerance time, i.e. how long the participant endures the pain. Participants end the test by raising their hands when they can no longer stand it or when the set end time of three minutes has elapsed.

Pressure algometry test

The pressure algometry test (31, 32) generates a mechanical pressure against specific points on the body; trapezius (shoulder), epicondyle (elbow), gluteal (outside the gluteal muscle) and medial knee (inside of the knee) which are all accepted in the diagnosis of fibromyalgia. Pressure algometry tests are measured in kilopascal (kPa). The Trial Manager interrupts the mechanical pressure when the participant expresses pain.

Numeric rating scale (NRS)

Participants rate their pain intensity on NRS (33) in connection with the Cold Pressor Test when the participant takes her hand from the water, after one minute and finally after three minutes. Participants estimate their pain intensity on a scale (NRS) from 0-10, where 0 corresponds to no pain at all and 10 worst possible pain. Pain rating is measured in the same way after the pressure algometry test.

The influence of expectation, desire for pain relief, and pain variability will be measured before each injection using the same numeric rating scale as used for pain ratings. Ratings of expected pain levels will be obtained by asking patients “What level of pain do you expect when this treatment starts to have an effect?” The NRS scale is anchored at the left by the descriptors ‘no pain sensation’ and at the right by ‘the most pain sensation imaginable’. Ratings of desired pain relief will be obtained by asking patients “How strong is your desire for pain relief? The question will be anchored by the descriptors ‘0=No desire for pain relief’ and ‘10=the most intense desire for pain relief imaginable’. Ratings of pain variability will be obtained by asking participants their average pain intensity that week. These scales have been validated and used in previous studies (35-39).

Short-form McGill Pain Questionnaire (MPQ)

In this study MPQ Short form of 15 questions (26) is used which distinguishes between the sensory-discriminatory and the affective and emotional aspects of the pain experience. Participants are asked to estimate their pain intensity and describe their pain in predetermined words. They fill in MPQ on all three measurement occasions.

RAND-36

RAND-36 is a quality-of-life instrument (27) that aims to measure health-related quality of life, i.e. physical, mental and social well-being and not merely the absence of illness. The estimation instrument consists of 36 questions of various kinds, e.g. on general health, activity, physical health,

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3 emotional problems and pain. RAND-36 is filled in by the participant on all
4 three measurement occasions.
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8 Patient Global Impression of Change (PGIC)

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10 PGIC (34) evaluates participants' experience of the treatment i.e. the
11 substance given. Participants tick the box that most closely describes the
12 change that they are experiencing. The PGIC is completed by the participant
13 after the injection treatment has been concluded at 12 weeks and at the
14 follow-up 12 weeks later. PGIC is directly translated in its entirety from
15 English by the research group.
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22 Cobalamin/p

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24 Cobalamin/p levels are taken on three occasions: at the first measurement,
25 baseline, in order to rule out that none of the participants has a Vitamin B12
26 deficiency (according to the accepted reference value). At the second
27 measurement, at 12 weeks on completion of treatment in order to monitor the
28 participants' level of cobalamin/p just after the end of the injection treatment.
29 The final measurement is 12 weeks after the end of intervention.
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33 Qualitative in-depth interview

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35 In order to obtain a deeper understanding of women's perceived experiences,
36 in-depth interviews with both compliant and non-compliant participants from
37 both groups will be performed in connection with the third measurement
38 session. The aim is to describe the women's lived experiences of pain,
39 health, suffering and well-being. The interviews will be conducted by the
40 Trial Manager, recorded, transcribed and later analysed using a reflective life
41 world approach (RLR) (23).
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50 **Sample Size**

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52 In order to obtain an adequate sample size, a power analysis was performed
53 based on results from a previously published study (28) in which women
54 with the current diagnosis, fibromyalgia, underwent the same stimulation
55 procedure with the Cold Pressor Test. Account is taken here of the standard
56 deviation shown and compensation for any placebo effects. Based on these
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3 results, the expected effect difference is estimated at 20 seconds with a
4 standard deviation of 20 seconds between the two groups after 12 weeks of
5 treatment with Mecobalamin (Vitamin B12)/placebo. Using a two-sided
6 t-test for two independent groups, with a power of 80% and 5% significance
7 level, it was calculated that each group would consist of 16 participants. In
8 order to compensate for any loss, 20 participants per group are therefore
9 included. The study continues until 40 participants have been included and
10 completed the study.
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19 **Randomisation and allocation concealment**

20 Participants are randomised into two groups, the placebo group or the
21 treatment group, each consisting of 20 participants either receiving
22 Mecobalamin (Vitamin B12) or placebo (NaCl). An independent statistician
23 generates a randomisation list by random distribution of processing in blocks
24 (1:1) in a computerised statistics program (STATA). Participants are
25 randomised according to the list by the Chief Examiner opening closed
26 randomisation envelopes in consecutive order. Based on each randomisation
27 envelope, the Chief Examiner registers in and signs the injection retrieval
28 protocol as to which substance the participant will receive. The participants'
29 randomisation number is recorded in the journal. Only the Chief Examiner
30 has access to randomisation envelopes and injection retrieval protocols
31 which are kept locked.
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41 When the third measurement session has been completed, the Trial Manager
42 contacts the Chief Examiner who has the randomisation list.

43 The Chief Examiner breaks the code and notifies the participant by letter of
44 which substance she has been treated with. The code is broken at this time
45 because it cannot be considered ethical that the participant does not find out
46 about the treatment given, especially if the participant believes that the
47 treatment has helped. If the participant has received Mecobalamin and
48 wishes to continue, they are recommended to contact their health centre for
49 continued Mecobalamin treatment. The letter will contain the contact
50 information of the Trial Manager and the Chief Examiner if the health centre
51 doctor wishes to contact them. The Trial Manager is still unaware of what the
52 individual participant received until the study is completed. If the code needs
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3 to be broken for an individual participant before the third measurement
4 session has been completed, there is a code breaking envelope that may be
5 used by the Chief Examiner in cases of emergency.
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10 **Statistical methods**

11 The primary endpoint is tolerance time at Cold Pressor Test will be
12 calculated on the difference between the two groups after 12 weeks and will
13 be analysed by ANOVA. Pain thresholds measured by pressure algometry
14 test (Somedic) will be analysed using: t-test, ANOVA, similar to the primary
15 variable. Questionnaires (MPQ, RAND-36, and PGIC) will be analysed
16 using Mann-Whitney tests. In cases of minor loss, (less than 10%), a mixed
17 model can be used as an alternative to t-test and ANOVA with repeated
18 measurement. For variables with more than 10% loss, imputation of data will
19 be used. Drop-out participants will be described in a specific analysis.
20 Rejection analysis will be performed on the participants who interrupt the
21 study prematurely.
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32 The study will present results both from “intention to treat” and “per
33 protocol” analyses. Intention to treat" is defined as the participant is placed in
34 the treatment group she had been randomised to. "Per protocol" is defined as
35 the participant is placed in the treatment group she de facto received and
36 carried out without significant protocol deviations. “Per protocol” will be
37 presented as sensitivity analysis. The participant may miss a maximum of
38 two injections.
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46 Self-reported ratings of desired and expected treatment outcome pre and post
47 treatment will be implemented in linear regression models to predict any of
48 the outcome measures. Repeated ratings of desired treatment outcome,
49 expected treatment outcome and pain variability will be calculated as each
50 participant's standard deviation from the repeated ratings and implemented in
51 a linear regression model to predict possible outcome measures.
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ETHICS AND DISSEMINATION

The protocol for the study is approved by the local ethical committee at Linköping (EPM); 2018/294-31 (Appendix 2019-00347; 2020-04482) and the Swedish Medical Products Agency; EudraCT-no 2015-005086-23 (Appendix 5.1-2020-71076) furthermore monitored from Forum Ostergotland, Linköpings university. The study is registered at ClinicalTrials.gov: ID NCT05008042, follows Good Clinical Practice (GCP) and adheres to the principles of the Helsinki Declaration (2013) (40). All participants must give their written as well as oral consent to participate. They will be informed that they may discontinue the study whenever they wish to without giving any reason for their decision. The study started 6 of February 2019, recruiting is delayed caused by COVID-19. Trial results expects during 2024 and will be disseminated at national and international conferences, peer-reviewed journals, newsletters and magazines.

Discussion

The results of the study will investigate whether Vitamin B 12 decreases pain sensitivity and experience of pain in women suffering from fibromyalgia. The European Federation of the IASP (The international Association for the Study of Pain) (EFIC) Declaration from 2001 expressed that, “*very few people die of pain, many dies in pain and even more live in pain*”. To live in pain affects the whole human existence and people with chronic pain such as fibromyalgia often feel discredited, having to fight to assert their right to treatment and to receive the necessary care (2). Today, there is no curative treatment for fibromyalgia (41, 42). Since opioid analgesics, SNRI and gabapentinoids are the most used pharmacological treatments for Fibromyalgia, often with side effects (4, 10), there is a need for alternative treatments (11), with less side effects.

Furthermore, there is currently a lack of studies on patients' subjective experiences of living with long-term pain and fibromyalgia (43, 44), why it is important to evaluate the effect of Mecobalamin (Vitamin B12), and describe lived experiences of pain, health, suffering and well-being in women with diagnosed fibromyalgia.

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Contributors

KSH, GL, KS, JF, AWo, MP, KJ, BG and CE planned the study design and all authors participated in the production of the analysis plan. All authors participated in the acquisition of data. KSH, GL, KS and CE prepared the first version of the manuscript and all authors participated in reviewing and drafting the manuscript. All authors have read and approved the final version.

Conflict of interest

There are no conflicts of interest to report

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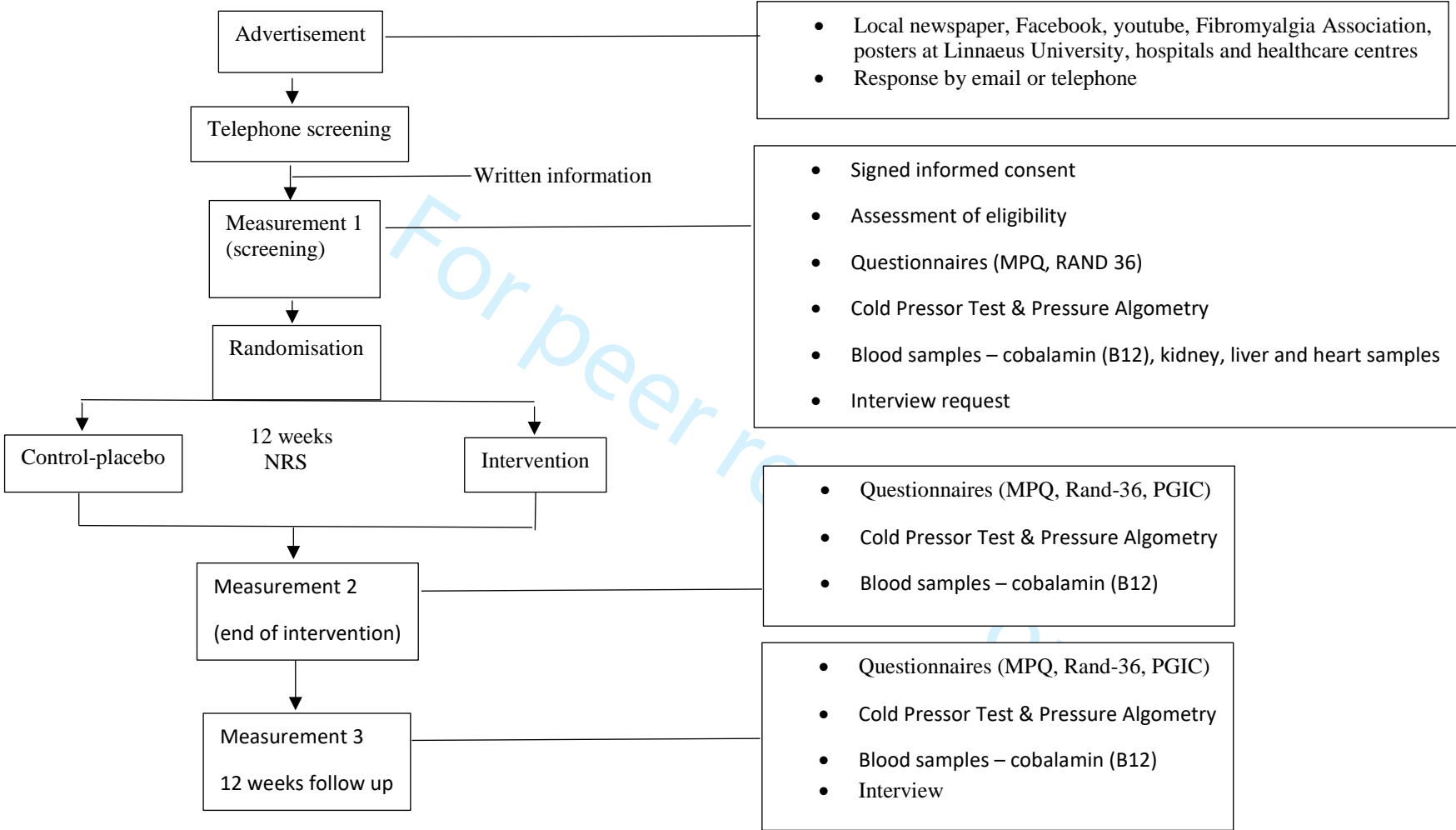


Fig 1. Flowchart of participants, outcome measures and follow-up points



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how
13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
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Methods: Data collection, management, and analysis

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21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol
27		18b	Plans to promote participant retention and complete follow-up,
28			including list of any outcome data to be collected for participants who
29			discontinue or deviate from intervention protocols
30			
31	Data	19	Plans for data entry, coding, security, and storage, including any
32	management		related processes to promote data quality (eg, double data entry;
33			range checks for data values). Reference to where details of data
34			management procedures can be found, if not in the protocol
35			
36	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
37	methods		Reference to where other details of the statistical analysis plan can be
38			found, if not in the protocol
39		20b	Methods for any additional analyses (eg, subgroup and adjusted
40			analyses)
41		20c	Definition of analysis population relating to protocol non-adherence
42			(eg, as randomised analysis), and any statistical methods to handle
43			missing data (eg, multiple imputation)
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Methods: Monitoring

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53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
54			and reporting structure; statement of whether it is independent from
55			the sponsor and competing interests; and reference to where further
56			details about its charter can be found, if not in the protocol.
57			Alternatively, an explanation of why a DMC is not needed
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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
7			spontaneously reported adverse events and other unintended effects
8			of trial interventions or trial conduct
9			
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11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
12			whether the process will be independent from investigators and the
13			sponsor
14			

Ethics and dissemination

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16			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board
18	approval		(REC/IRB) approval
19			
20			
21	Protocol	25	Plans for communicating important protocol modifications (eg,
22	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
23			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
24			regulators)
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
27			participants or authorised surrogates, and how (see Item 32)
28			
29		26b	Additional consent provisions for collection and use of participant data
30			and biological specimens in ancillary studies, if applicable
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33	Confidentiality	27	How personal information about potential and enrolled participants will
34			be collected, shared, and maintained in order to protect confidentiality
35			before, during, and after the trial
36			
37	Declaration of	28	Financial and other competing interests for principal investigators for
38	interests		the overall trial and each study site
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41	Access to data	29	Statement of who will have access to the final trial dataset, and
42			disclosure of contractual agreements that limit such access for
43			investigators
44			
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
46	post-trial care		compensation to those who suffer harm from trial participation
47			
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
49	policy		participants, healthcare professionals, the public, and other relevant
50			groups (eg, via publication, reporting in results databases, or other
51			data sharing arrangements), including any publication restrictions
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54		31b	Authorship eligibility guidelines and any intended use of professional
55			writers
56			
57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

For peer review only

BMJ Open

Efficacy of mecobalamin (vitamin B12) in the treatment of long-term pain in women diagnosed with fibromyalgia: protocol for a randomized, placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066987.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Jan-2023
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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Health services research, Pharmacology and therapeutics
Keywords:	COMPLEMENTARY MEDICINE, PAIN MANAGEMENT, QUALITATIVE RESEARCH, STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS

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Manuscripts

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3 **Efficacy of mecobalamin (vitamin B12) in the treatment of long-term**
4 **pain in women diagnosed with fibromyalgia: protocol for a randomized,**
5 **placebo-controlled trial**
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7 **ABSTRACT**

8 **Introduction**

9
10 Fibromyalgia causes long-term pain. It affects at least 2% of the population,
11 the majority being women. In addition, extended symptoms corresponding to
12 vitamin B12 deficiency occur. Findings from several studies have indicated
13 that vitamin B12 may be a possible treatment for pain in fibromyalgia. The
14 aim of the proposed study is to evaluate whether vitamin B12 decreases pain
15 sensitivity and the experience of pain (i.e. hyperalgesia and allodynia) in
16 women with fibromyalgia.
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23 **Methods and analysis**

24
25 The study is a randomized, placebo-controlled, single-blind, clinical trial
26 with two parallel groups who are administered mecobalamin (vitamin B12)
27 or placebo over 12 weeks. 40 Swedish women aged 20-70 years with an
28 earlier recorded diagnosis of fibromyalgia are randomized into the placebo
29 group or the treatment group, each consisting of 20 participants. Outcomes
30 consist of questionnaires measured at baseline and after 12 weeks of
31 treatment. A final re-evaluation will then follow 12 weeks after treatment
32 ends. The primary outcome is tolerance time, maximised to three minutes,
33 which is assessed using the Cold Pressor Test. In order to broaden the
34 understanding of the lived experience of participants, qualitative interviews
35 will be conducted using a phenomenological approach on a life-world
36 theoretical basis (Reflective Lifeworld Research approach).
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48 **Ethics and dissemination**

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50 The protocol for the study is approved by the local ethical committee at
51 Linköping (EPM); 2018/294-31 (Appendix 2019-00347; 2020-04482). The
52 principles of the Helsinki Declaration are followed regarding oral and written
53 consent to participate, confidentiality and the possibility to withdraw
54 participation in the study at any time. The results will primarily be
55 communicated through peer-reviewed journals and conferences.
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Trial registration numbers: EudraCT, 2015-005086-23 (Appendix 5.1-2020-71076), protocol no 2020-08-17 version 5.0; ClinicalTrials.gov, NCT05008042.

Keywords: Fibromyalgia, Cobalamin, Chronic pain, Mekoalamin, Randomized controlled trial, Vitamin B12

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study design is a randomized, placebo-controlled, single-blind clinical trial using parallel groups.
- The trial is a collaboration between different universities and regions.
- A possible limitation is the low number of participants; however, the study continues until 20 participants per group have been included and completed the study, which exceeds the minimum number of 16 determined in our power calculation.
- Another possible limitation is heterogeneity of fibromyalgia spectrum.
- Another possible limitation is the placebo effects of parenteral injection; however, the participants are individually randomized to intervention or control group (placebo) in 1:1 allocation ratio.

INTRODUCTION

Fibromyalgia causes long-term pain and affects at least 2% of the population, 80% of the sufferers being women (1). Treatment options are scarce and patients with fibromyalgia have experienced being discredited and invalidated by the health-care system (2). Fibromyalgia is characterized by long-term widespread musculoskeletal pain and generalized hyperalgesia. This is often accompanied by fatigue, concentration problems and sleep problems (3).

Fibromyalgia pain is currently classified as nociplastic, which means that pain arises from altered regulation of pain signals, in absence of tissue damage (4). No definite pathophysiology has been established for fibromyalgia. Imaging techniques have challenged previous ideas about the

1
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3 peripheral origin of FM and have provided evidence for altered central
4 nervous system (CNS) nociceptive/pain processing and morphology in
5 fibromyalgia. Furthermore, recent studies report both central alterations and
6 peripheral alterations (e.g., systemic low-grade inflammation and
7 nociceptor/muscle alterations) (5-9)

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Current treatment for fibromyalgia includes both non-pharmacological and pharmacological interventions, depending on the key symptoms and the extent of disability. The recommended pharmacological treatments for fibromyalgia are antidepressants (e.g. SNRI) and antiepileptics (e.g. gabapentinoids), which often cause side effects (4). In addition, opioid analgetics and NSAID/COX are often prescribed (10). Only a minority of individuals report a clinically relevant improvement from any of the treatments (11).

Vitamin B12 is sometimes used for symptoms other than those of vitamin B12 deficiency e.g., different pain conditions such as backpain and neuropathic pain (12-16). Vitamin B12 nasal drops have been tested with positive results on patients with ME/CF/fibromyalgia (myalgic encephalomyelitis/chronic fatigue syndrome) (17). A recent study showed that sublingual vitamin B12 had positive effect on patients with fibromyalgia (18).

In addition, there are vitamin B12 studies that have shown good results in the therapy of aphthous ulcers (19) and acute lumbago (20) as well as in studies concerning diabetic polyneuropathy (21, 22). Moreover, studies examining methylcobalamin treatment in patients with lower back pain showed pain reduction and functionality gain (13, 23).

To summarize, it is not entirely clear how vitamin B12 affects the human pain system. However, several studies indicate that it may be a possible treatment in fibromyalgia.

Aim and objectives

The aim of this study is to evaluate the effect of mecobalamin (vitamin B12), and describe lived experiences of pain, health, suffering and well-being in women with diagnosed fibromyalgia.

The primary objective is to evaluate whether mecobalamin (vitamin B12) given as an intramuscular injection once/week for 12 weeks compared to placebo reduces pain sensitivity i.e. tolerance time (Cold Pressor Test).

The secondary objective is to evaluate whether intramuscular mecobalamin (vitamin B12) compared to placebo reduces pain intensity and pressure pain threshold (Numeric rating scale NRS, Pressure Algometry), increases activity level (questionnaire), quality of life (questionnaire) and perceived effect of given drug (questionnaire). Furthermore, the ratings of expected effects of a given drug (NRS), the desire for pain relief (NRS) and estimated pain variability (NRS) are evaluated. Qualitative interviews that describe how women with fibromyalgia experience pain, health, suffering and well-being (interviews) will be conducted.

METHODS AND ANALYSIS

Study design

The study is an academic randomized, placebo-controlled, single-blind clinical trial using parallel groups. Participants are individually randomized to intervention or control group (placebo) in 1:1 allocation. In order to broaden and deepen the understanding of the lived experience, an interview will be conducted applying a phenomenological approach on a life-world theoretical basis, Reflective Lifeworld Research approach (RLR) (24).

Study setting and sample

Swedish women aged 20-70 years with an earlier recorded diagnosed fibromyalgia. Detailed eligibility criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none"> - Diagnosis of fibromyalgia - Women aged 20-70 years - Swedish-speaking - Safe method of contraception - Cobalamin value >250 pmol/L < 800 pmol/L 	<ul style="list-style-type: none"> - Previous treatment with B12 - Known hypersensitivity to the active substance mecobalamin or an additive - Neuroleptic treatment - Reynaud's phenomenon - Known neuropathy

<ul style="list-style-type: none"> - Kidney function value (relatively) GFR >60 mL/min/1.73 m² - Liver function value P-ALP 0.6-2.85 µkat/L P-ALAT 0.15-1.13 µkat/L - Heart function value Troponin-T < 15 ng/L NT-pro-BNP < 60 years <125 ng/L NT-pro-BNP > 60 years < 300 ng/L - Given consent to participate 	<ul style="list-style-type: none"> - Vegan as veganism can lead to B12 deficiency - Known heart, kidney or liver disease - Breastfeeding - Planned or ongoing pregnancy
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The participants are recruited via advertising in the local newspaper Facebook, YouTube, Fibromyalgia Association, posters at Linnaeus University, hospitals and healthcare centres. The prospective participant contacts the Trial Manager via telephone or email and receives oral information. Written information and consent form (Supplemental File) are sent to the participant who contacts the Trial Manager for an appointment.

Intervention and placebo

The active substance of vitamin B12 given in the study is 2ml mecobalamin (5mg/ml) intramuscularly (25). Placebo substance is 2 ml Sodium Chloride (9 mg/ml), isotonic solution for parenteral use (Baxter) intramuscularly (26). All participants are informed that their urine may turn red, which may occur during mecobalamin injections.

Measurements

At the first measurement opportunity, the trial manager and co-examiner 1 carefully follow inclusion and exclusion criteria. Oral information is given again, and consent is signed by the participant and by the co-examiner 1. First, the participant answers two questionnaires Short-form McGill Pain Questionnaire (MPQ) (27) and RAND 36 (28), then stimulation tests (Cold Pressor Test, pressure algometry) (29 - 33) are performed followed by pain rating (NRS) (34) immediately, after one minute and after three minutes.

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3 Finally, blood samples for cobalamin (vitamin B12), kidney, liver and heart
4 markers are taken. The participant provides an information card about the
5 study's design, purpose, treatment options and contacts with telephone
6 numbers. The participant is asked about interest in an interview in connection
7 with the final measurement opportunity. Co-examiner 2 assesses the blood
8 samples and approves final inclusion. If tests deviate from accepted reference
9 values, the participant is excluded and encouraged to seek medical attention.
10 After approved inclusion, an independent chief examiner performs the
11 randomisation. The participant then receives intramuscular injections of the
12 active substance or placebo, once a week for 12 weeks, given by a registered
13 nurse. Before each injection the participant answers questions in which they
14 estimate their expected effects of a given drug, desire for pain relief and
15 average pain intensity during the past week (NRS). The participant has the
16 opportunity to postpone the visit \pm 3 days, for example in case of illness or
17 travelling and may miss a maximum of two injections in order to follow per-
18 protocol analysis. Even if the participant is not compliant with the study
19 protocol, the participant may retain the treatment regime for the duration of
20 the study and be analysed in the main intention-to-treat analysis.
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34 The second measurement takes place after 12 weeks of
35 intervention and three questionnaires (MPQ, RAND 36) and (Patient Global
36 Impression of Change PGIC) (35) are filled out. The stimulation tests Cold
37 Pressor Test and pressure algometry are performed as well as blood sampling
38 of cobalamin/p (vitamin B12). In cases of low cobalamin/p, the participant is
39 encouraged to seek medical attention but is still included in the study.
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45 At the third measurement, which takes place 12 weeks after the
46 end of the intervention, the participant fills in questionnaires (MPQ, RAND-
47 36 and PGIC), undergoes stimulation tests (Cold Pressor Test and pressure
48 algometry), blood sampling of cobalamin/p (vitamin B12) together with an
49 interview. If cobalamin/p on this occasion shows that the participant has a
50 low cobalamin value, the participant is encouraged to seek medical attention.
51 For the individual participant, the study ends after six months. An overview
52 of the study flow is presented in Figure 1.
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Outcomes

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3 The primary outcome is:
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- 5 • Tolerance time, maximised to three minutes, which is tested using the
6 Cold Pressor Test.
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9 The secondary outcome are:
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- 11 • Pain experience measured by a pressure algometry test performed on
12 the shoulder, hip, knee and elbow.
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- 14 • Possible pain change measured by a pressure algometry test
15 performed on the shoulder, hip, knee and elbow.
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- 17 • Subjective experience of pain measured using Numeric Rating Scale
18 (NRS) 0-10 where 0 is the best outcome.
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- 20 • Possible pain change measured using Numeric Rating Scale (NRS) 0-
21 10 where 0 is the best outcome.
22
- 23 • Ratings of expectation, desire for relief, using Numeric Rating Scale
24 (NRS) 0-10 where 0 is the best outcome.
25
- 26 • Ratings of expectation, pain variability, using Numeric Rating Scale
27 (NRS) 0-10 where 0 is the best outcome.
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- 29 • Activity level are assessed using questionnaire McGills Pain
30 Questionnaire (MPQ). Short version score 0-45.
31
- 32 • Quality of life are assessed using questionnaires RAND-36 score 0-
33 100.
34
- 35 • Experience of the effect of the drug, assessed using questionnaire
36 Patients' Global Impression of Change (PGIC) score 1-7.
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- 38 • Control of vitamin B12 is done by measuring cobalamin in plasma.
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- 40 • Qualitative in-depth interviews will be conducted to capture women's
41 lived experiences of pain, health, suffering and well-being.
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51 Cold Pressor Test

52 The Cold Pressor Test (29-31) is measured in number of seconds the
53 participant leaves her hand in the low-temperature water of five degrees.
54 Evaluation variables from Cold Pressor Test become pain threshold (when it
55 starts to hurt) and tolerance time, i.e. how long the participant endures the
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3 pain. Participants end the test by raising their hands when they can no longer
4 stand it or when the set end time of three minutes has elapsed.
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8 Pressure algometry test

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10 The pressure algometry test (32, 33) generates a mechanical pressure against
11 specific points on the body; trapezius (shoulder), epicondyle (elbow), gluteal
12 (outside the gluteal muscles) and medial knee (inside of the knee) which are
13 all accepted in the diagnosis of fibromyalgia. Pressure algometry tests are
14 measured in kilopascal (kPa). The Trial Manager interrupts the mechanical
15 pressure when the participant expresses pain.
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22 Numeric rating scale (NRS)

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24 Participants rate their pain intensity on NRS (34) in connection with the Cold
25 Pressor Test when the participant takes her hand from the water, after one
26 minute and finally after three minutes. Participants estimate their pain
27 intensity on a scale (NRS) from 0-10, where 0 corresponds to no pain at all
28 and 10 worst possible pain. Pain rating is measured in the same way after the
29 pressure algometry test.
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34 The influence of expectation, desire for pain relief, and pain
35 variability will be measured before each injection using the same numeric
36 rating scale as used for pain ratings. Ratings of expected pain levels will be
37 obtained by asking patients “What level of pain do you expect when this
38 treatment starts to have an effect?” The NRS scale is anchored at the left by
39 the descriptors ‘no pain sensation’ and at the right by ‘the most pain
40 sensation imaginable’. Ratings of desired pain relief will be obtained by
41 asking patients “How strong is your desire for pain relief? The question will
42 be anchored by the descriptors ‘0=No desire for pain relief’ and ‘10=the most
43 intense desire for pain relief imaginable’. Ratings of pain variability will be
44 obtained by asking participants their average pain intensity that week. These
45 scales have been validated and used in previous studies (36-40).
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56 Short-form McGill Pain Questionnaire (MPQ)

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58 In this study MPQ Short form of 15 questions (27) is used which
59 distinguishes between the sensory-discriminatory and the affective and
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3 emotional aspects of the pain experience. Participants are asked to estimate
4 their pain intensity and describe their pain in predetermined words. They fill
5 in MPQ on all three measurement occasions.
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10 RAND-36

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12 RAND-36 is a quality-of-life instrument (28) that aims to measure health-
13 related quality of life, i.e. physical, mental and social well-being, not just the
14 absence of illness. The estimation instrument consists of 36 questions of
15 various kinds, e.g. on general health, activity, physical health, emotional
16 problems and pain. RAND-36 is filled in by the participant on all three
17 measurement occasions.
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25 Patient Global Impression of Change (PGIC)

26 PGIC (35) evaluates participants' experience of the treatment i.e. the
27 substance given. Participants tick the box that most closely describes the
28 change that they are experiencing. The PGIC is completed by the participant
29 after the injection treatment has been concluded at 12 weeks and at the
30 follow-up 12 weeks later. PGIC is directly translated in its entirety from
31 English by the research group.
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39 Cobalamin/p

40 Cobalamin/p levels are taken on three occasions. The first measurement,
41 baseline rule out a vitamin B12 deficiency (according to the accepted
42 reference values). A second measurement is performed at 12 weeks on
43 completion of treatment in order to monitor the participants' level of
44 cobalamin/p just after the end of the injection treatment. The final
45 measurement is 12 weeks after the end of intervention.
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52 Qualitative in-depth interview

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54 In order to obtain a deeper understanding of women's perceived experiences,
55 in-depth interviews with both compliant and non-compliant participants from
56 both groups will be performed in connection with the third measurement
57 session. The aim is to describe the women's lived experiences of pain,
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3 health, suffering and well-being. The interviews will be conducted by the
4 Trial Manager, recorded, transcribed and later analysed using a reflective life
5 world approach (RLR) (24).
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10 **Sample size**

11 In order to obtain an adequate sample size, a power analysis was performed
12 based on results from a previously published study (29) in which women
13 with fibromyalgia underwent the same stimulation procedure with the Cold
14 Pressor Test. Account is taken here of the standard deviation shown and
15 compensation for any placebo effects. Based on these results, the expected
16 effect difference is estimated at 20 seconds with a standard deviation of 20
17 seconds between the two groups after 12 weeks of treatment with
18 mecobalamin (vitamin B12)/placebo. Using a two-sided
19 t-test for two independent groups, with a power of 80% and 5% significance
20 level, it was calculated that each group would consist of 16 participants. In
21 order to compensate for any loss, 20 participants per group are therefore
22 included. The study continues until 40 participants have been included and
23 completed the study.
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36 **Randomization and allocation concealment**

37 Participants are randomized into two groups, the placebo group or the
38 treatment group, each consisting of 20 participants either receiving
39 mecobalamin (vitamin B12) or placebo. An independent statistician
40 generates a randomisation list by random distribution of processing in blocks
41 (1:1) in a computerised statistics program (STATA). Participants are
42 randomized according to the list by the chief examiner opening closed
43 randomisation envelopes in consecutive order. Based on each randomisation
44 envelope, the chief examiner registers in and signs the injection retrieval
45 protocol as to which substance the participant will receive. The participants'
46 randomisation number is recorded in the journal. Only the chief examiner has
47 access to randomisation envelopes and injection retrieval protocols which are
48 kept locked.
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58 When the third measurement session has been completed, the
59 trial manager contacts the chief examiner who has the randomisation list.
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3 The chief examiner breaks the code and notifies the participant with a letter
4 of given treatment. The code is broken at this time because it cannot be
5 considered ethical that the participant does not find out about the treatment
6 given, especially if the participant believes that the treatment has helped. If
7 the participant has received mecobalamin and wishes to continue, they are
8 recommended to contact their health centre for continued mecobalamin
9 treatment. The letter will contain the contact information of the trial manager
10 and the chief examiner if the health centre doctor wishes to contact them.
11
12 The trial manager is still unaware of what the individual participant received
13 until the study is completed. If the code needs to be broken for an individual
14 participant before the third measurement session has been completed, there is
15 a code breaking envelope that may be used by the chief examiner in cases of
16 emergency.
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28 **Adverse events (AEs) and serious adverse events (SAEs)**

29 AEs are defined as any unfavourable or unintended reaction occurring in a
30 research person during the course of the study and where investigational
31 medicinal products have been administered, regardless of dose. Any AE will
32 be reported from day 1 of the study at each visit to the clinic and until the last
33 visit made 24 weeks after the start of the study. All SAEs that occur during
34 the course of the study will be reported to the sponsor within 24 hours of the
35 research staff becoming aware of the incident. During the study, an annual
36 safety report from the sponsor and responsible investigator is sent in to both
37 the Swedish Medical Products Agency and the Regional Ethical Review
38 Board.
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48 **Statistical methods**

49 The primary endpoint is tolerance time at Cold Pressor Test and it will be
50 calculated on the difference between the two groups after 12 weeks and will
51 be analysed by ANOVA. Pain thresholds measured by pressure algometry
52 test (Somedic) will be analysed using: t-test, ANOVA, similar to the primary
53 variable. Questionnaires (MPQ, RAND-36, and PGIC) will be analysed
54 using Mann-Whitney tests. In cases of minor loss, (less than 10%), a mixed
55 model can be used as an alternative to t-test and ANOVA with repeated
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3 measurement. For variables with more than 10% loss, imputation of data will
4 be used. Drop-out participants will be described in a specific analysis.
5 Rejection analysis will be performed on the participants who interrupt the
6 study prematurely.
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10 Results will be reported for both intention-to-treat and per-
11 protocol analyses. Intention-to-treat is defined as the participant is placed in
12 the treatment group she had been randomized to. Per-protocol is defined as
13 the participant is placed in the treatment group she de facto received and
14 carried out without significant protocol deviations. The per-protocol results
15 will be presented as sensitivity analyses. The participant may miss a
16 maximum of two injections.
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22 Self-reported ratings of desired and expected treatment
23 outcome pre and post treatment will be implemented in linear regression
24 models to predict any of the outcome measures. Repeated ratings of desired
25 treatment outcome, expected treatment outcome and pain variability will be
26 calculated as each participant's standard deviation from the repeated ratings
27 and implemented in a linear regression model to predict possible outcome
28 measures.
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36 **Patient and public involvement**

37 None.
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41 **ETHICS AND DISSEMINATION**

42 The study is registered at the Swedish Medical Products Agency, EudraCT-
43 no 2015-005086-23 (Appendix 5.1-2020-71076), protocol no 2020-08-17
44 version 5.0 and ClinicalTrials.gov (NCT05008042). The trial was approved
45 by the local ethical committee at Linköping (EPM); 2018/294-31 (Appendix
46 2019-00347; 2020-04482). The principles of the Helsinki Declaration (2013)
47 (41) are followed regarding oral and written consent to participate,
48 confidentiality and the possibility to withdraw participation in the study at
49 any time. Good Clinical Practice (GCP) is followed, with independent
50 regular monitoring by Forum Ostergotland, Linköpings University, including
51 plans for communicating important protocol modifications. The data will be
52 placed in a locked cabinet at the university until the study is completed and
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3 the data is to be processed and analysed. Only involved researchers have
4 access to data when it is to be analysed; however, anyone requesting
5 metadata can access the data during 2025-2035. The study started on
6 February 6th, 2019, but recruitment was delayed due to the COVID-19
7 pandemic. Final recruitment is expected to be completed in 2024. The results
8 will primarily be communicated through peer-reviewed journals and
9 conferences.
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18 19 20 **Contributors**

21 KSH (trial manager), GL, KS, JF (chief examiner), MP, KJ, BG and CE
22 (sponsor) planned the study design and all authors participated in the
23 production of the analysis plan. KSH, GL, KS, AWo and CE prepared the
24 first version of the manuscript and all authors participated in reviewing and
25 drafting the manuscript. All authors have read and approved the final
26 version.
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32 33 34 **Competing interests**

35 There are no conflicts of interest to report.
36
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45 manuscript.
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Figure title

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Figure 1. Flowchart of participants, outcome measures and follow-up points

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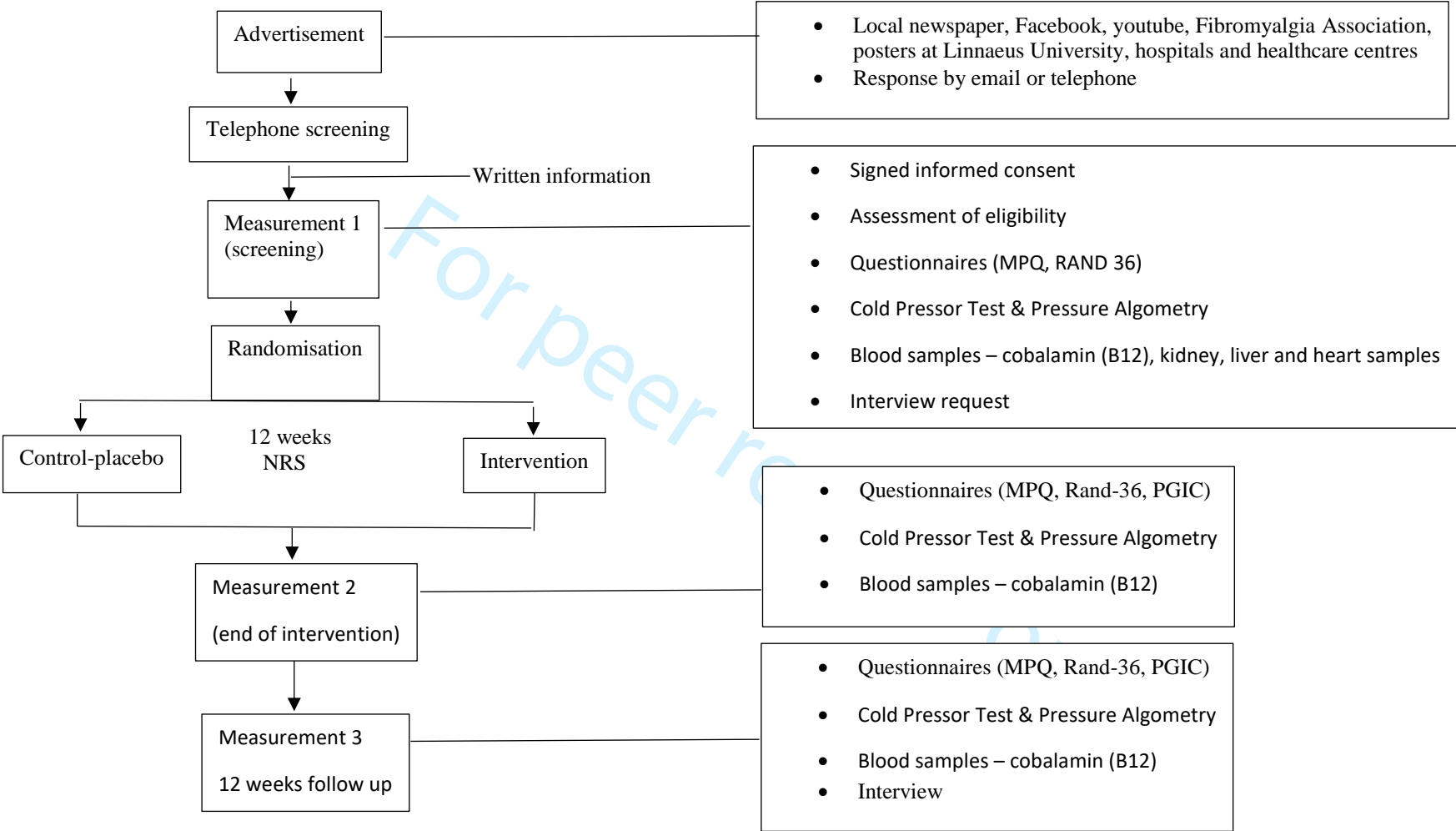


Fig 1. Flowchart of participants, outcome measures and follow-up points

Participant informed consent form

I have been informed orally about the study and I have read the written information. I have received answers to my questions and I agree to participate in the study. My participation is voluntary, and I am aware that I can withdraw without any explanation and without affecting my future care.

I am informed about my rights to get register extract once a year over collected data. I have been informed about my rights to get false information's arranged or removed from the register. I have been informed about samples taken in the study are handled according to the Biobank Act. I am aware that my sample material will be destroyed after analyses.

Consent regarding data management

I have received information that personal data collected in the study will be handled confidentially, which means my identity will not be revealed to unauthorized persons.

I allow an independent person and/or authority person, appointed by the study management, to review study information provided customary confidentiality are maintained.

We ask you to confirm your identity at all occasions with legitimation.

.....
Participants' signature Date (written by participant)

.....
Name clarification

.....
Physician signature Date

.....
Name clarification

Signed copy of the information and consent has been distributed to the participant.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3 and 14
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	Page 3 and 14
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 1 and 15

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	Page 3-5
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____
7				
8	Objectives	7	Specific objectives or hypotheses	Page 5
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	Page 6
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	Page 5
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	Page 6-8
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	Page 6-8
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	Page 6-8
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	Page 8 - 11
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	Page 6-8 - fig 1
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 6
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 12
11	generation			
12				
13				
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16	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 12
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 12
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 12
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 12
28				
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31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 9-11
34	methods			
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 13
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12 -14
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13-14
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 13-14
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13-14
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14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 14
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 13
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 14
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 14
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7 and 14
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 12 and 14
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 14
14				
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 15
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 14
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 7 and 14
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.